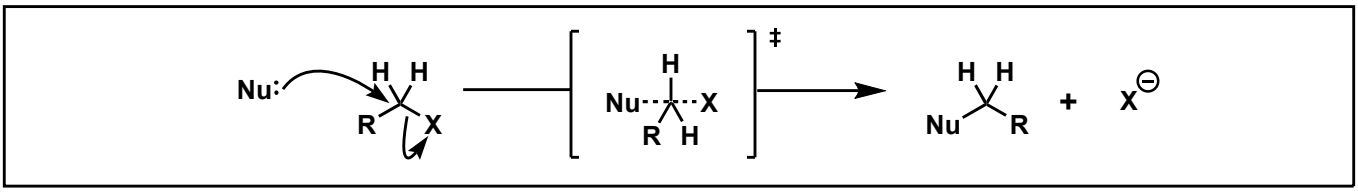
Chemistry 17: Section Handout 8

Topics: *substitution mechanisms at sp^3 carbons, S_N1/S_N2, determination of substitution mechanism pathways, elimination (E1, E2, E1cB), the E1 / E2 / S_N1 / S_N2 continuum*

Key Concept Review

Nucleophilic Substitution at sp^3-Hybridized Carbon: When a good leaving group is attached to an sp^3-hybridized carbon, it is possible to perform a substitution reaction in which the leaving group is replaced by a nucleophile. These reactions can proceed by an S_N1 or S_N2 mechanism.

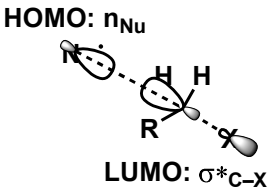
***S_N2 Mechanism*:** The S_N2 mechanism proceeds in a concerted manner, with nucleophilic attack and leaving group departure occurring simultaneously.



Considerations for an S_N2 mechanism:

- ***Steric hindrance:*** S_N2 reactions can happen at sp^3 carbons that are not sterically crowded, for example at primary carbons.

- ***Orbital analysis:*** The HOMO must approach the LUMO at 180° to maximize the orbital overlap. Because of the concerted nature of the mechanism and the required nucleophilic approach, this is a st*ereospecific re*action and always proceeds with inversion of configuration at the sp^3 carbon.

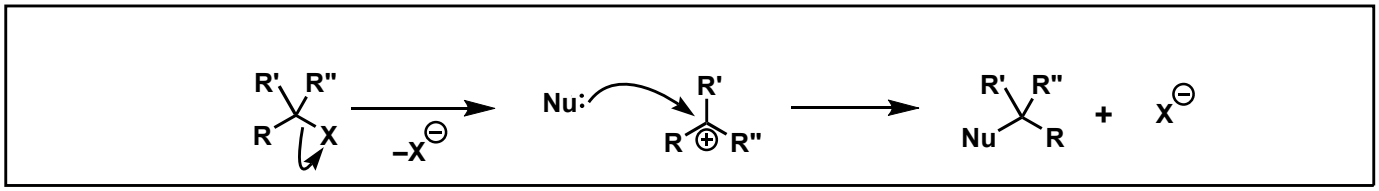


- ***Nucleophile strength:*** The rate equation of an S_N2 mechanism is represented as rate = k[Nu][substrate]. Because the rate of an S_N2 reaction depends on the nucleophile and the substrate, stronger and more reactive nucleophiles will accelerate the rate of an S_N2 pathway.

- ***Leaving group ability:*** Non-basic, stable leaving groups will accelerate an S_N2 reaction.

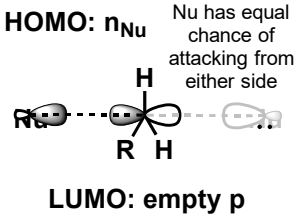
- ***Solvent effects:*** Polar, aprotic solvents (DMF, DMSO, acetone) will accelerate S_N2 reactions due to their inability to stabilize a strong, anionic nucleophile.

S_N1 Mechanism: The S_N1 mechanism proceeds in a stepwise manner, with departure of the leaving group occurring in the first step to afford a carbocation. Nucleophilic attack on the carbocation occurs in the second step.



Considerations for an S_N1 mechanism:

- ***Orbital analysis:*** The nucleophile's HOMO can approach the LUMO from either face of the planar carbocation intermediate. Because of the trigonal planar geometry of carbocation intermediates, the configuration in the starting material is lost and nucleophilic attack gives a racemic mixture of products.

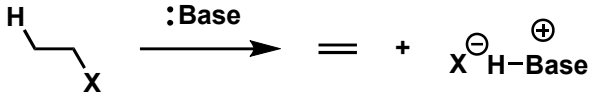


• ***Carbocation stability:*** S_N1 reactions are successful only when a stable carbocationic intermediate can be generated, for example through resonance stabilization or hyperconjugation. Due to hyperconjugation, 3° carbocations are more stable than 2° carbocations.

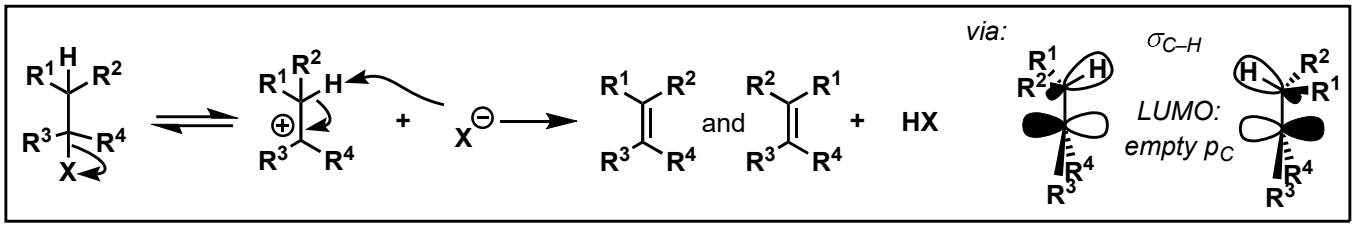
• ***Leaving group ability:*** *T*he rate-determining step of an S_N1 reaction is the first step (ionization), and the rate equation is rate = k[substrate]. Non-basic, stable leaving groups will accelerate an S_N1 pathway.

• ***Solvent effects:*** Polar, protic solvents (alcohols, carboxylic acids, water) will accelerate S_N1 reactions by stabilizing an anionic leaving group.

Elimination Reactions: Elimination reactions result in the loss of a leaving group and an adjacent H-atom to form a double bond. Elimination reactions may proceed through an E1, E2, or E1cb mechanism.



E1 Mechanism: The E1 mechanism proceeds in a stepwise manner, with the departure of the leaving group occurring in the first step to afford a carbocation (this is the same as the first step of an SN1 mechanism). Deprotonation at the site adjacent to the carbocation occurs in the second step. Because rotation can occur about the central C–C bond in the carbocation intermediate, a mixture of (E) and (Z) alkene products forms. The rate-determining step of an E1 reaction is the first step, and the rate equation is represented as rate = k[R–X]. E1 and SN1 mechanisms often compete, forming a mixture of products.



• C*arbocation Stability: E1* reactions are successful only when a stable carbocation intermediate can be generated. Due to hyperconjugation, 3° leaving groups afford the most stable carbocations, while 2° carbocations are only moderately stable. Benzylic and allylic carbocations are also exceptionally stable due to their resonance delocalization of the positive charge. 1° leaving groups generally do not participate in E1 mechanism.

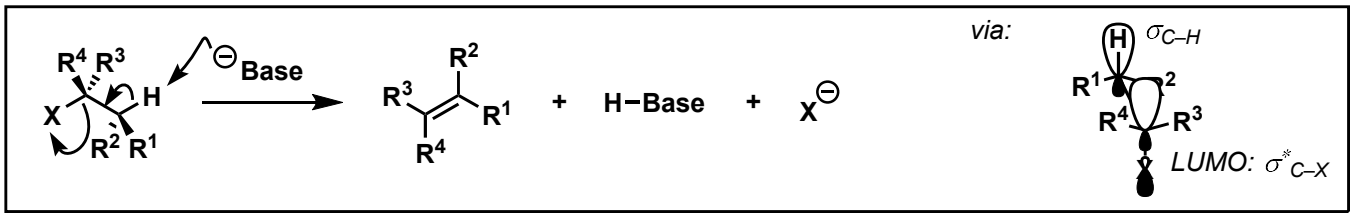
• A*lkene Stability: In* situations where the carbocation can eliminate to form more than one alkene product, the most stable alkene is usually formed preferentially. In general, (E) alkenes are more stable than their (Z) counterparts for steric reasons. More-substituted alkenes are also more stable than their less-substituted counterparts due to the hyperconjugation from the substituent $\sigma_{C–H}$ or $\sigma_{C–C}$ orbitals with the $\pi^*_{C–C}$ orbital.

• L*eaving Group Ability:* Good leaving groups will accelerate an E1 mechanism.

• B*ase Strength:* Weak bases, like water, alcohols, or halides favor E1 mechanisms.

• S*olvent Effects:* Polar, protic solvents will accelerate the E1 mechanism by stabilizing the anionic leaving group, thereby facilitating carbocation formation.

E2 Mechanism: The E2 mechanism proceeds in a concerted manner, with deprotonation and leaving group departure occuring simultaneously. The reactive H and X atoms must be oriented antiperiplanar to each other in order for the σ_{C-H} orbital to overlap with the σ^*_{C-X} orbital. Due to these precise geometric requirements for the concerted transition state, the reaction is stereospecific and the alkene configuration (E or Z) in the product depends on the configuration of the starting material. The rate equation of an E2 reaction is represented as rate = k[R–X][Base].



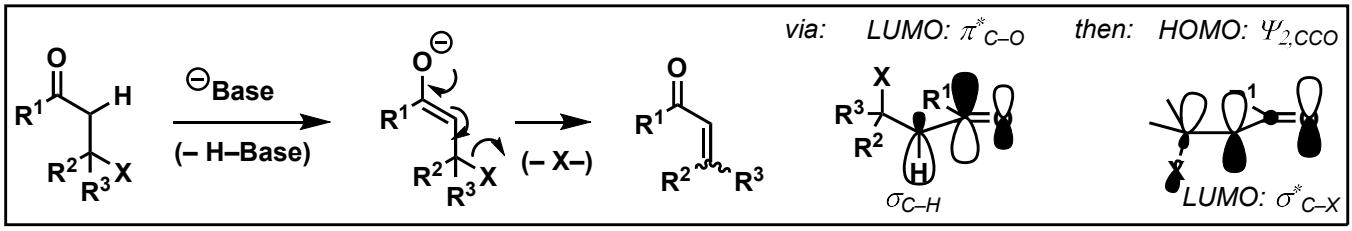
• B*ase Strength: St*rong bases like alkoxides or metal hydrides (NaH, KH) facilitate E2 elimination over E1 elimination and/or SN2 substitution.

• S*teric Hindrance:* Bulky substrates and bulky bases (especially bulky alkoxides like ⁻Ot-Bu*)* favor elimination over substitution, and hindered bases will preferentially form less-substituted alkene products.

• L*eaving Group Ability: Go*od leaving groups will accelerate an E2 mechanism.

• S*olvent Effects: Po*lar, aprotic solvents will accelerate the E2 mechanism due to their inability to stabilize the strong, anionic base.

E1cB Mechanism: The E1cB mechanism proceeds in a stepwise manner, with the deprotonation of the substrate occurring in the first step to afford a stabilized anionic intermediate. Departure of the leaving group to form a conjugated alkene occurs in the second step.



• *Leaving Group Ability:* The E1cB mechanism can proceed even with poor leaving groups.

• *Anion Stability:* The E1cB mechanism can only proceed when α-H is acidified to a significant extent by an adjacent π-withdrawing group, usually a carbonyl

The S_N1-S_N2-E1-E2 Continuum: for some reactions, it will be possible for both substitution and elimination reactions to happen under the same conditions, generating mixtures of products. However, most reactions will generate a major product from the most favored reaction pathway (S_N1/S_N2/E1/E2). Some factors to consider are:

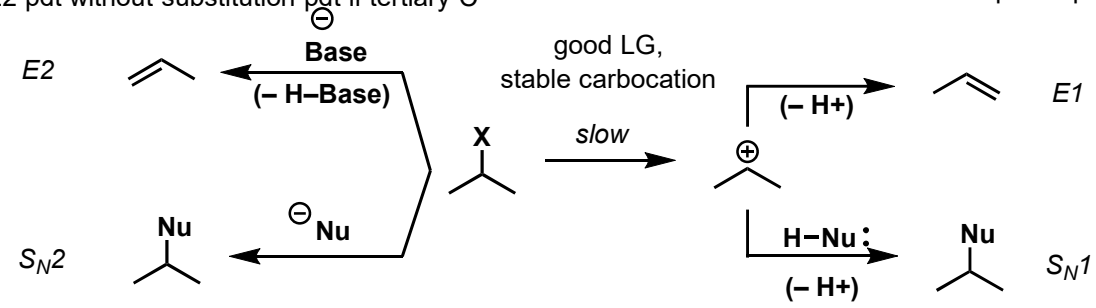
• *Ionization Rate:* Ionization to a carbocation is slow. If a bimolecular reaction (S_N2 or E2) that avoids the ionization process is possible, it will be much faster than ionization (S_N1 or E1).
• *Base Strength: The* basicity of the nucleophile will largely determine whether the reaction will favor substitution or elimination pathways. Strong bases will favor elimination through an E2 mechanism, while weak bases will favor S_N1/E_1 mechanisms.
• *Steric Hindrance: Bulky* substrates and bulky bases favor elimination over substitution.
• *Solvent Effects: Polar, a*protic solvents favor S_N2/E2 mechanisms, while protic solvents favor S_N1/E1 mechanisms.

Bulky base

need H antiperiplanar to LG

Will get E2 pdt without substitution pdt if tertiary C

Can get E1 product alone if in acid and no sufficient nucleophiles present



S_N2 only product if:

Nu not particularly basic but very nucleophilic (RS^-/RSH)

No protons to remove alpha to the LG

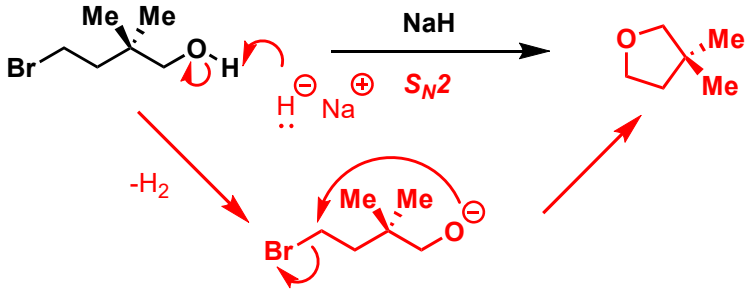
Can favor S_N1 if there are no protons in the alpha position in addition to the other requirements

Workshop Problems

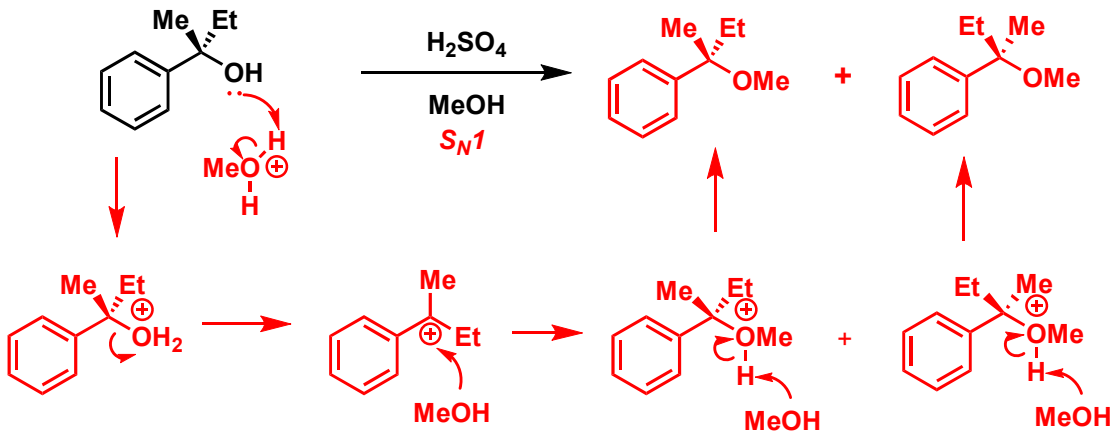
Workshop Problem 1: S_N1 and S_N2 Reactions

For each of the following reactions, predict the product and provide an arrow-pushing mechanism for its formation. Label each mechanism as S_N1 or S_N2 and provide all possible stereoisomers of the product.

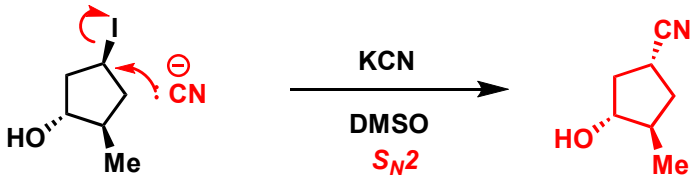
1-a **Note: NaH is a very strong base, pK_{aH} of hydride ion is 35.**



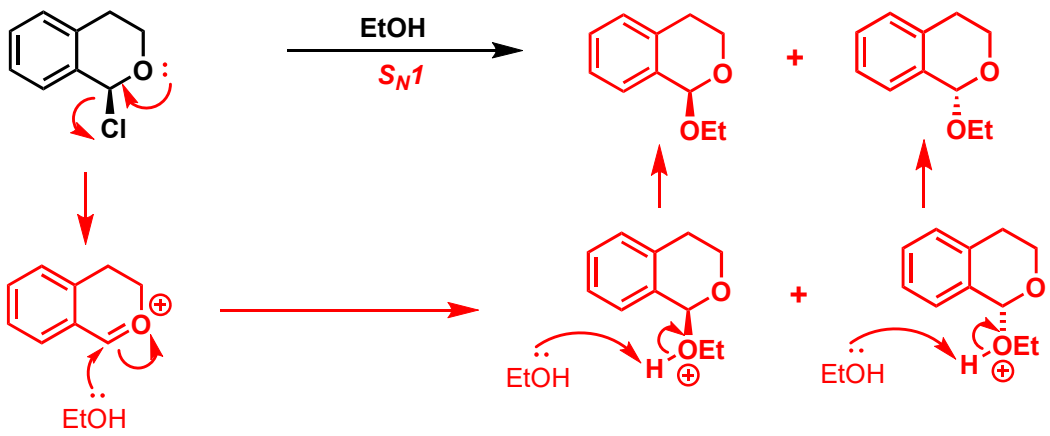
1-b



1-c.


I
CN
HO
Me
KCN
DMSO
S_N2
CN
HO
Me

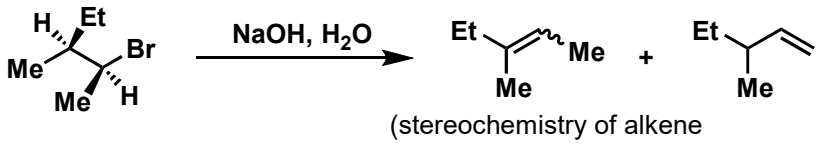
1-d

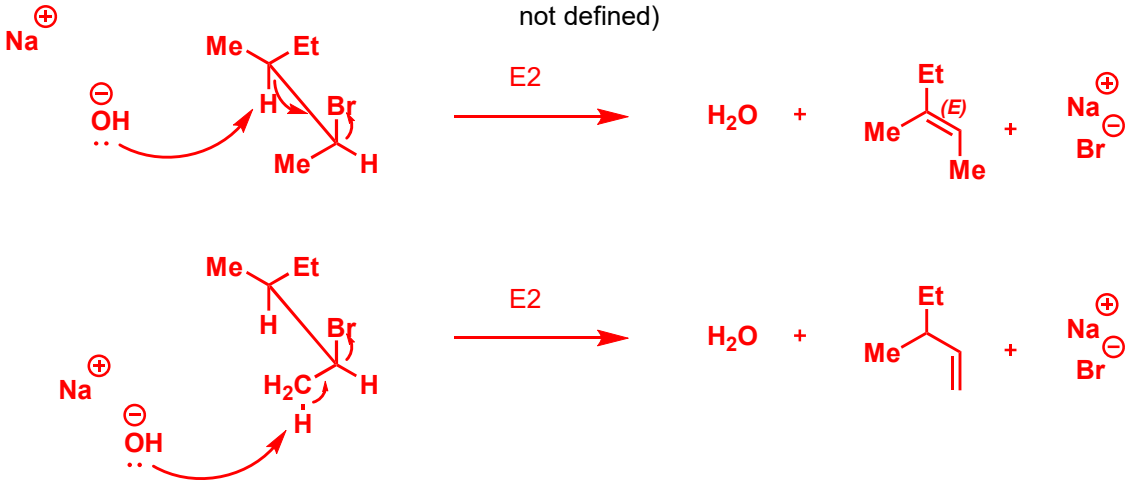

O
Cl
EtOH
S_N1
O
OEt
+
O
OEt
O
EtOH
O
OEt
H
+
O
EtOH
O
OEt
H

Workshop Problem 2: Elimination Mechanisms

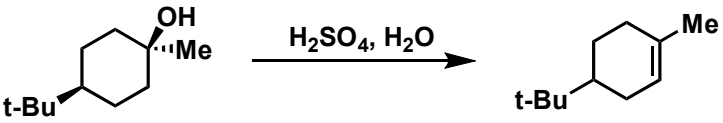
For each reaction below, propose a mechanism to account for the formation of the provided product(s), showing all of the reactant and intermediates in their reactive conformations, and using curved arrows to represent the redistribution of electron density in each step. Indicate whether the mechanism is E1 or E2. Redraw the product(s) with the appropriate stereochemistry, labeling each alkene as (*E*) or (*Z*).

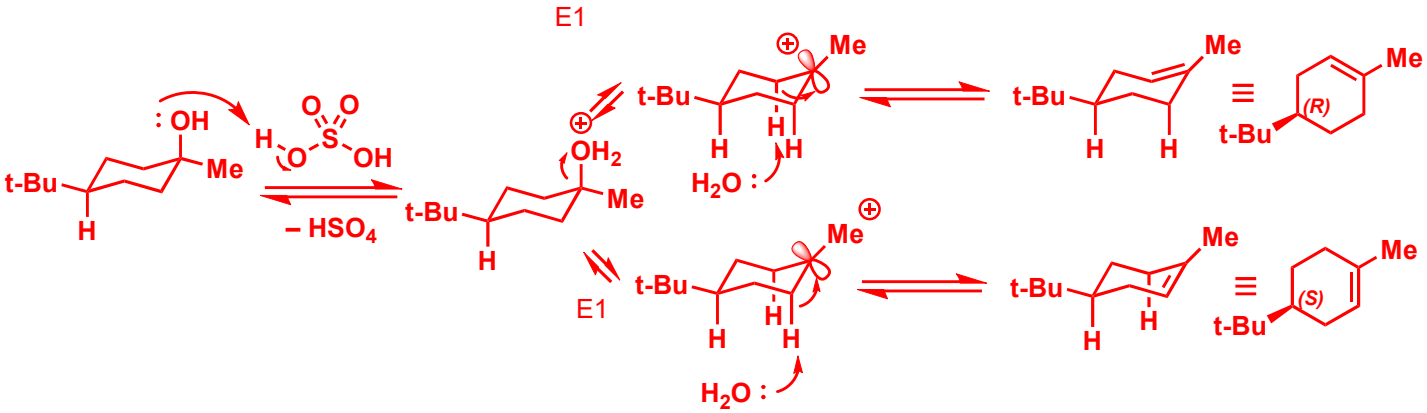
2-a.





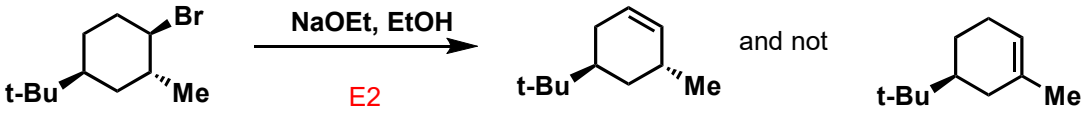
2-b.

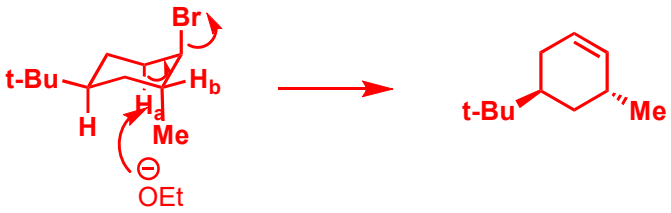




Do NOT worry about the conformations of the cyclohexene products!

2-c.



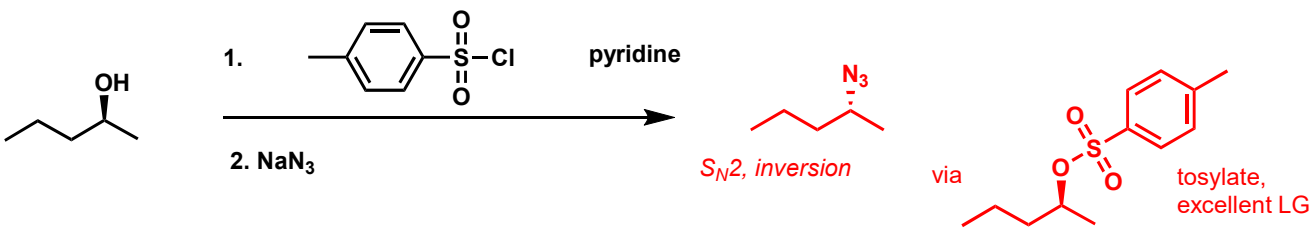


Elimination is only possible from H_a as H_b cannot be antiperiplanar to the Br leaving group

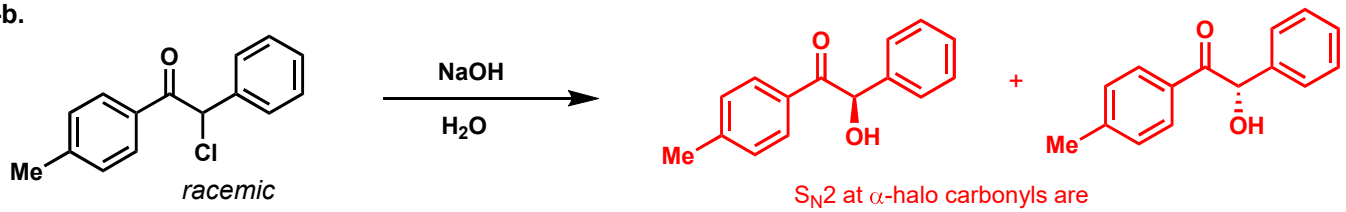
Practice Problems

Skillbuilder Problem 1: For each of the following reactions, predict the product(s) formed. Label each mechanism as S_N1 or S_N2 and provide all possible stereoisomers of the product.

1-a.

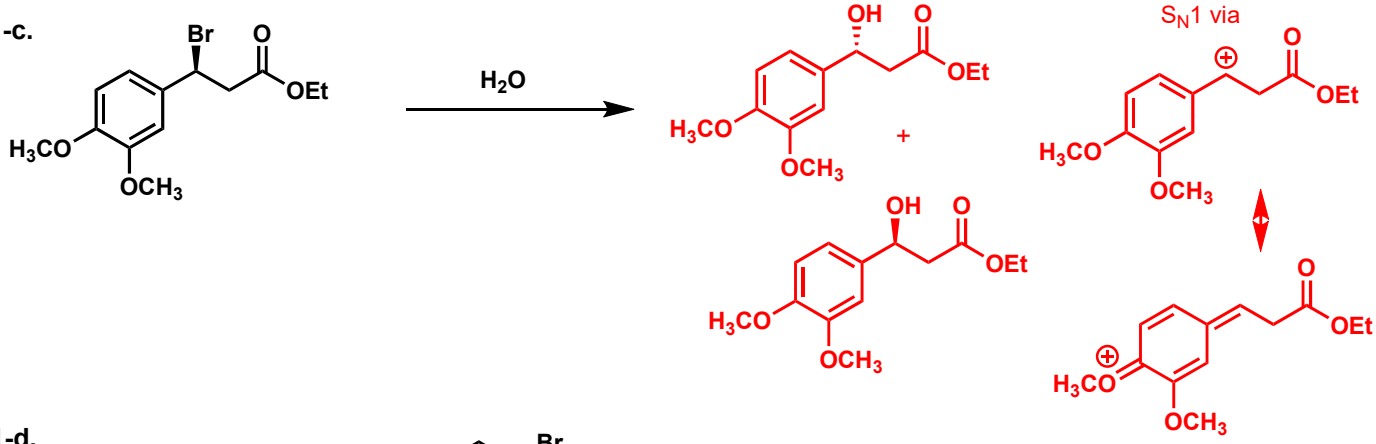


1-b.

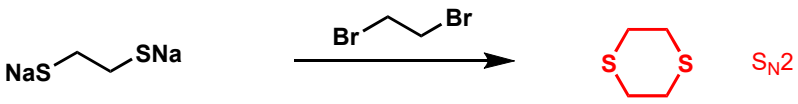


S_N2 at α-halo carbonyls are very favorable

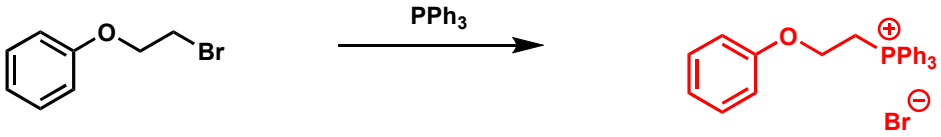
1-c.



1-d.

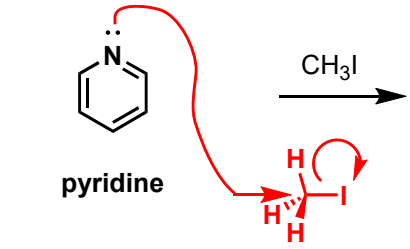


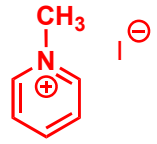
1-e.



S_N2 : P is polarizable. Neutral PR_3 compounds are good-excellent Nu

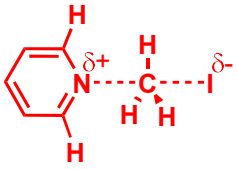
Skillbuilder Problem 2: The reaction of pyridine with methyl iodide is 50x faster than the corresponding reaction between lutidine and methyl iodide. Draw the reaction products and an arrow-pushing mechanism in each case, identify the reaction mechanism as either S_N1 or S_N2, and explain the difference in rate between the two reactions. Identify the HOMO and LUMO in each reaction.

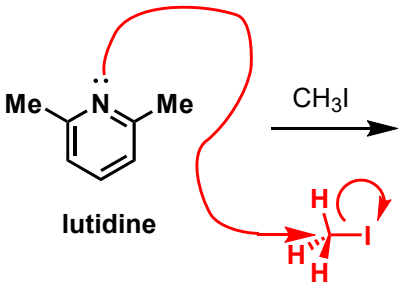


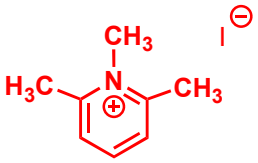


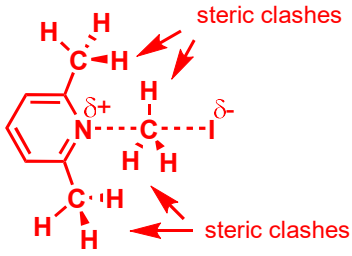
both S_N2, methyl substrates are the best for S_N2 and unable to undergo S_N1.

Transition state structures









The transition state for lutidine is more crowded and therefore higher energy and thus the reaction rate is slower. There are unfavorable steric interactions between the methyl groups adjacent to the nitrogen that make approach of the N to the backside of the C-I bond less favorable.

both reactions:
HOMO: n_N
LUMO: $\sigma^*_{C\text{-}I}$

Challenge Problem 1:
Consider the following reaction:

1-a. Is this reaction likely to proceed by an S_N1 or S_N2 mechanism? Explain.

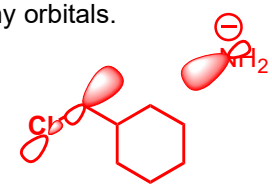
A leaving group attached to a primary carbon will be displaced via an S_N2 mechanism.

1-b. Provide a rate law for this reaction.

rate = k[alkyl chloride][$NaNH_2$]

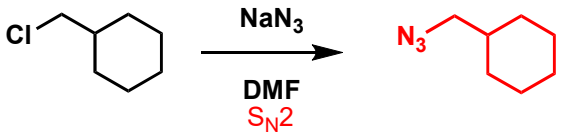
1-c. Draw and label the molecular orbital(s) involved in the transition state of this reaction. Include the appropriate sizes,
phasing, and geometry of any orbitals.

LUMO: $\sigma^*_{C\text{-}Cl}$

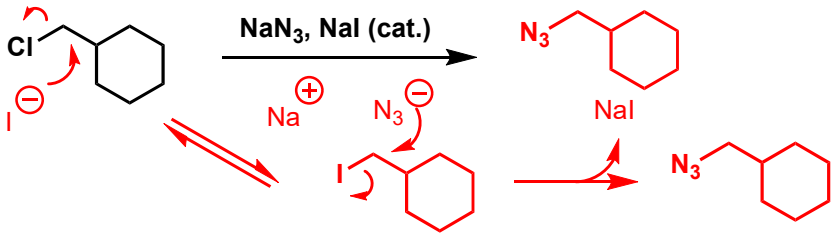


HOMO: n_N

1-d. Azides offer an alternative synthetic route to amine products. Provide the product of the following reaction, and identify the mechanism as S_N1 or S_N2.

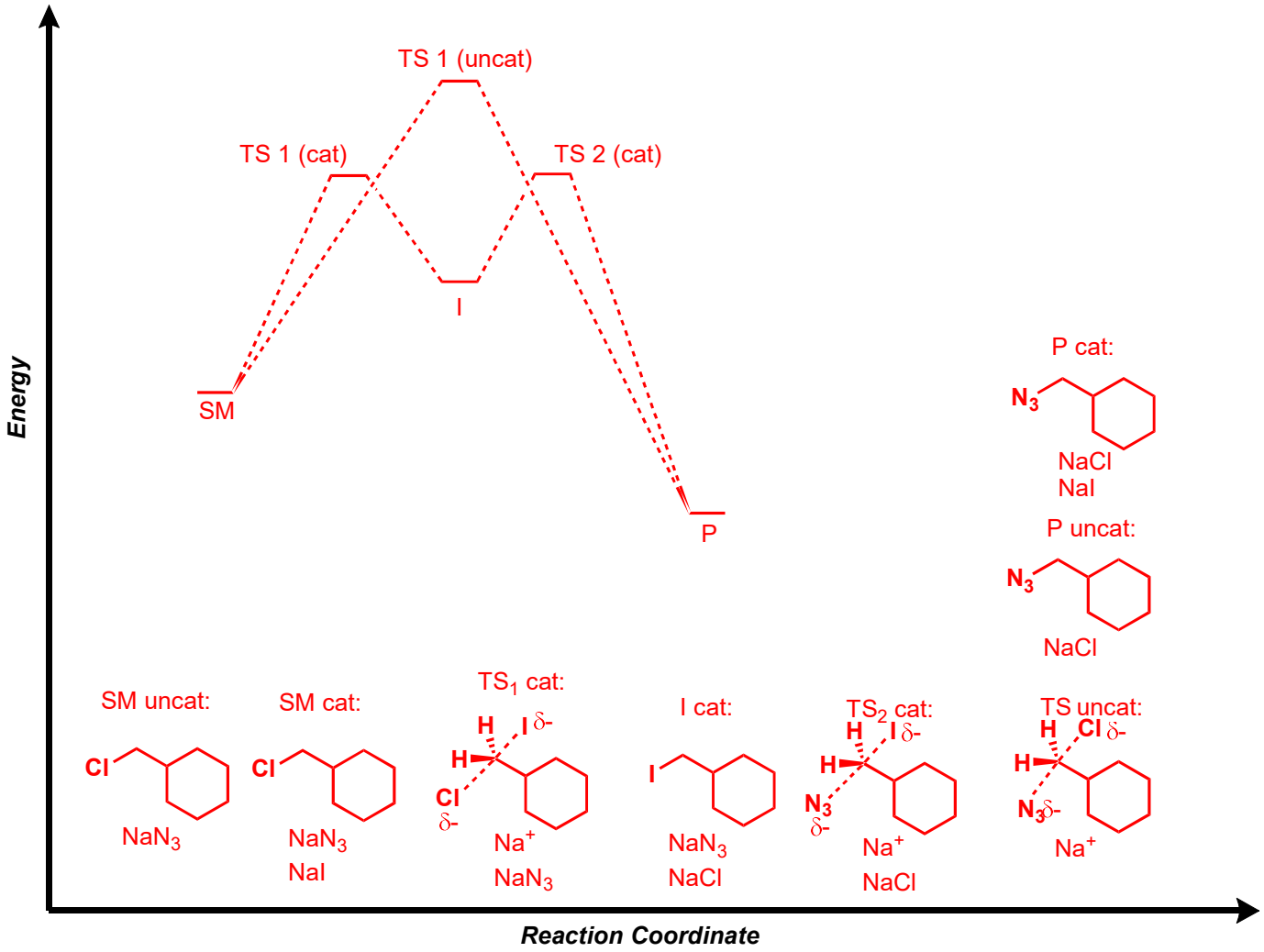


1-e. The rate of this reaction can be increased by adding a catalytic amount of sodium iodide. Provide a mechanism for this catalytic reaction, explicitly showing the regeneration of catalyst. Explain the observed rate acceleration.



Iodide is a better nucleophile and a better leaving group than azide and chloride, respectively. Increasing nucleophile strength increases the rate of an S_N2 reaction. Departure of the leaving group occurs in the rate determining step, so a better leaving group increases the rate of the reaction.

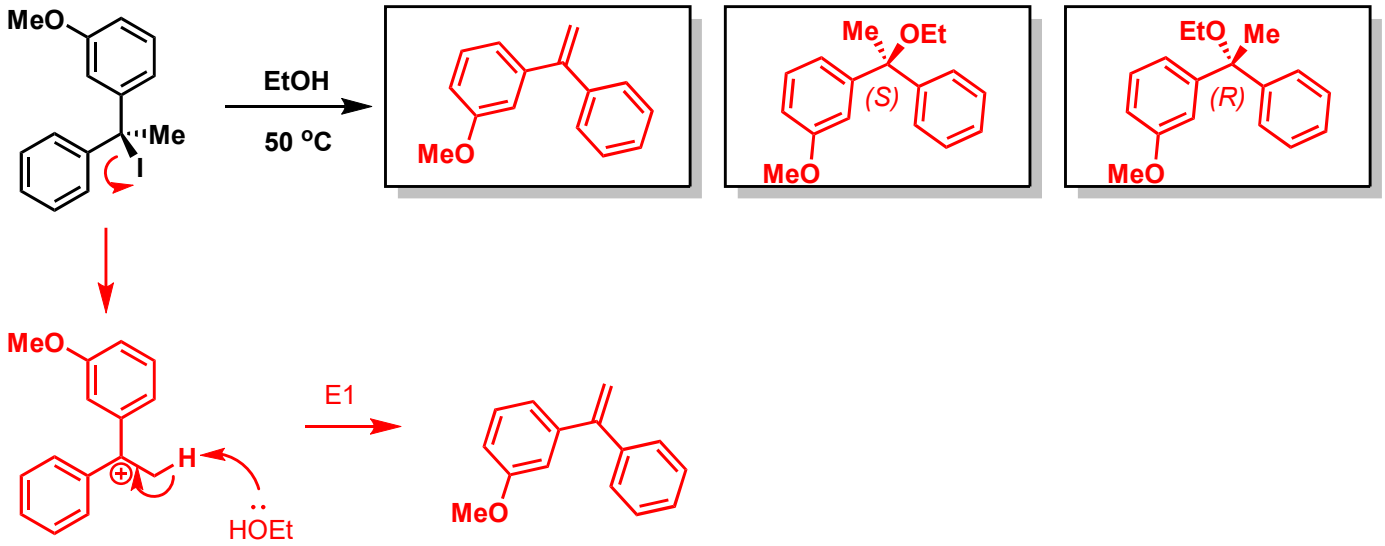
1-f. On the axes below, draw a qualitative free energy diagram for both the catalyzed and uncatalyzed reaction. Label and sketch ALL reactants, intermediates, transition states (TS_1, TS_2, TS_3 . . .), and products, and clearly place them at the correct relative energy levels.

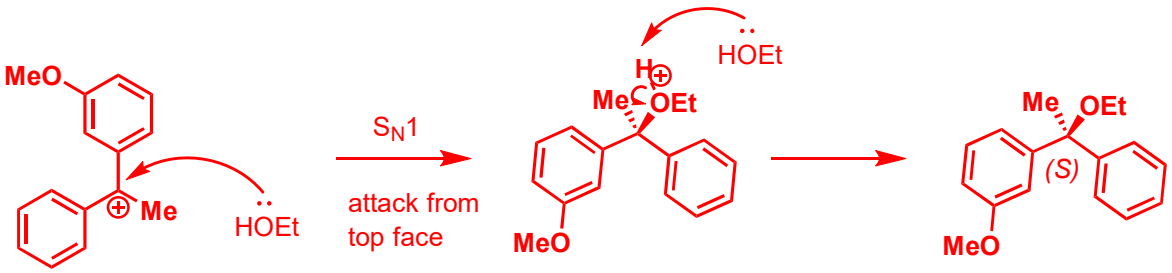


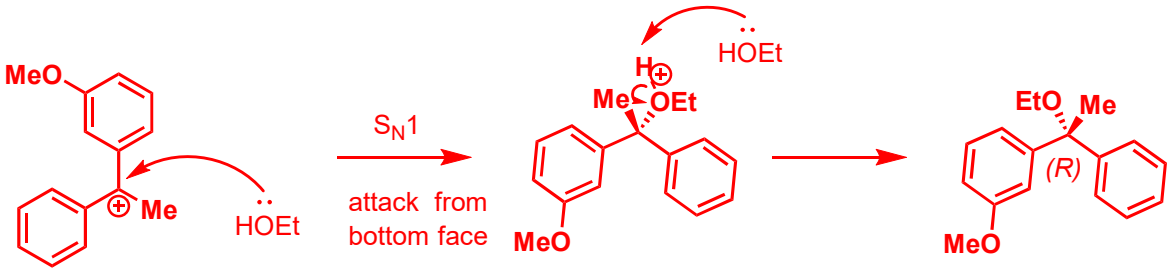
Challenge Problem 2

Sometimes, multiple reactions may proceed under the same conditions, but often the conditions may be altered to favor one product or another.

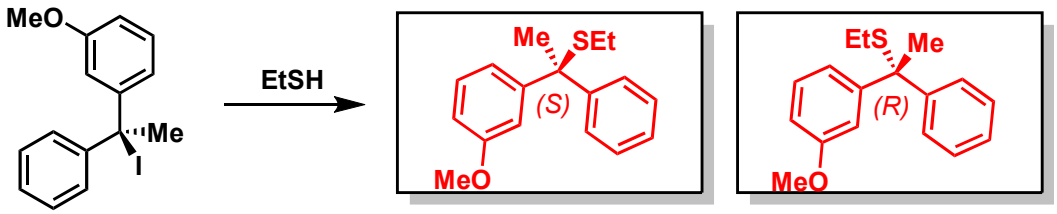
2-a. The following reaction conditions yield three products. Provide a mechanism for the formation of each of these products, using curved arrows to represent the redistribution of electrons in each step. Label each mechanism as $S_N1/S_N2/E1/E2$. In the products, label each stereocenter as (*R)* or (*S*).





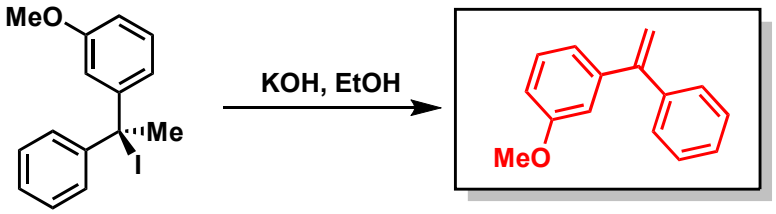


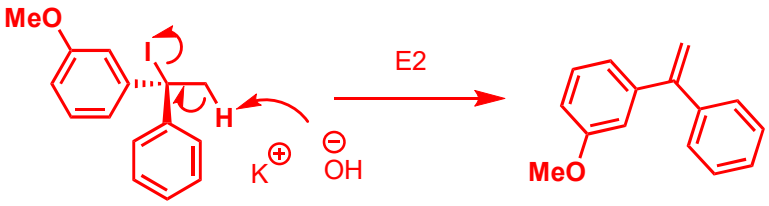
2-b. The conditions below yield only two products analogous to those formed in part **a**. Provide the structure for these two products. Justify why the product distribution differs from that observed in part **a**.



EtOH is a weak nucleophile and a weak base. After formation of the carbocationic intermediate in a, EtOH was capable of adding to or deprotonating that intermediate, generating a mixture of products. In contrast, EtSH is a better nucleophile and worse base than EtOH (S is less electronegative and more polarizable than O), so it is much more likely to act as a nucleophile and attack the carbocationic intermediate than it is to act as a base and deprotonate it. As a result, only substitution products are formed.

2-c. The conditions below yield only one of the products formed in part **a**. Provide a mechanism for the formation of this product, using curved arrows to represent the redistribution of electrons in each step. Justify why the product distribution differs from that observed in part **a**.





Ionization to form a carbocation (the first step of an S_N1 or E1 reaction) is slow and energetically unfavorable. When a strong base such as KOH is added, the E2 mechanism will proceed instead. Because the tertiary iodide is hindered, the S_N2 pathway will not be operative. As a result, only the elimination product is formed.